REMARKS

Upon entry of the present amendment, claims 54, 57-59, 61-69, 88-93, and 95-135 will be pending in the application. Claim 54 has been amended to include the limitations previously recited in claim 94, which has been canceled. Claims 99-135 are newly added. New claims 99-103 are supported by the specification at, for example, page 27, lines 17-21. New claims 104-135 are supported throughout the specification (*e.g.*, at page 24, line 3 through page 27, line 16). No new matter has been added.

35 U.S.C. § 112, ¶ 1

Claims 54, 57-59, 61-69, and 88-98 (all of the previously pending claims) have been newly rejected as failing to comply with the enablement requirement (Office action at pages 2-8). In view of the present amendment and the remarks that follow, this ground for rejection should be withdrawn.

The Examiner begins by reviewing the factors to be considered in determining whether a disclosure enables one of ordinary skill in the art to make and use the invention claimed, referencing *Ex parte Forman*, 230 USPQ 546 (BPAI 1986), *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988), and the MPEP. The Examiner reviews the factors to be considered in analyzing enablement, beginning with the quantity of experimentation necessary and concluding with the breadth of the claims. In view of the present amendment and because "all questions of enablement are evaluated against the claimed subject matter" (MPEP at 2164.08), Applicants turn first to the breadth of the claims.

As noted above, independent claim 54 (from which claims 57-59, 63-91, 95-100, 104-126, and 133-135 depend or ultimately depend) has been amended to include the limitations formerly recited in claim 94. Claim 54 now covers only those fusion proteins that include one of the seven specified influenza antigens, or an antigenic portion thereof, and one of the specifically recited stress proteins, or a portion thereof. In addition, the claim requires the fusion protein to induce an immune response against the antigen in a mammal to whom the fusion protein is administered. The claimed subject matter is thus limited in its nature (it must be a protein), in its

content (it must include one of each of the two recited components), and in its function (it must induce an immune response). The stress protein required by claim 61 (from which claims 62, 63, 92, 93, 101-103, and 127-132 depend or ultimately depend) must be a bacterial stress protein. The term "portion" certainly increases the scope of the claims in which it appears but, for the reasons that follow, not to such an extent that one of ordinary skill in the art would be forced to resort to undue experimentation. The "portion" must be a portion of one of the recited influenza antigens or stress proteins, the sequences of which are available to those of ordinary skill in the art and were at the time the instant application was filed. Applicants' specification also describes routinely practiced methods that were can be used to construct any fusion protein within the scope of the claims and assays that demonstrate induction of an immune response. Accordingly, we now review some of the direction provided by the specification, including one of Applicants' working examples.

In characterizing the amount of direction Applicants provided, the Examiner found "[n]one" other than a description of "general knowledge in the art" (Office action at page 6, last line, to page 7, line 1). Applicants do provide direction, and the amount of that direction is appropriate for the subject matter now claimed. A fusion protein is not a complicated thing. Moreover, neither of the polypeptides within the claimed fusion proteins were new. Applicants stated, "[s]tress genes and proteins for use in the present invention are those well known in the art" (specification at page 24, lines 3-4). They then go on to describe a number of suitable stress proteins (specification at pages 24-27). The methods for making fusion proteins were also well known, and Applicants not only referred to those methods but incorporated standard laboratory manuals describing them into the specification. Applicants state (specification at page 32, lines 13-23):

> The construction of expression vectors and the transfer of vectors and nucleic acids into various host cells can be accomplished using genetic engineering techniques, as described in manuals like *Molecular Cloning* and *Current Protocols in Molecular Biology*, which are hereby incorporated by reference, or by using commercially available kits (Sambrook, J., *et al.*, *Molecular Cloning*, Cold Spring Harbor Press, 1989; Ausubel, F.M., *et al.*, *Current Protocols in Molecular Biology*, Greene Publishing Associates and Wiley-Interscience, 1989)).

As further evidence that those of ordinary skill in the art routinely make and use fusion proteins, and that they did so at the time the present application was filed, Applicants' representative searched the PubMed database available through the National Center for Biotechnology Information (NCBI; www.ncbi.nlm.nih.gov) with the words "fusion" and "protein". As of today's date, almost 100,000 papers included those words and about 30,000 of those were published before 1996. While some of these are bound to be irrelevant for the present purpose, the sheer volume of publications in the field indicates the prevalence of fusion proteins and the familiarity those of skill in the art must have with them. As the Examiner acknowledged, the specification does not need to disclose what is well known to those of ordinary skill in the art (Office action at page 3, citing the MPEP at 2164.05(a), 6th paragraph).

Applicants' working examples add significantly to the specification. The Examiner's attention is kindly directed to the specification at page 45, where Applicants describe the preparation of fusion proteins that include a stress protein (a mycobacterial hsp65) and a portion of an influenza antigen (NP). One of the fusion proteins contains the amino acid sequence VQLASNENMETM, which is represented by SEQ ID NO:1 and corresponds to residues 363-374 of the complete NP protein disclosed in Motal *et al.* (*Eur. J. Immunol.* 25:1121-1124, 1995) and the references cited therein (specification at page 39, lines 16-17). This sequence includes an H-2b CTL epitope and is referred to as NP.B. Applicants also generated a fusion protein including a stress protein and, as a portion of an influenza antigen, residues 147-155 of NP (as disclosed in Levi and Arnon (*Vaccine* 14:85-92, 1996) (specification at page 45, lines 9-11). This antigen is referred to as NP.D. Applicants describe plasmid vectors used to express the fusion proteins (specification at pages 45-46), and these are illustrated in the detailed plasmid maps provided as Figs. 4A and 4B. The plasmids were transformed into a common cell type (an *E. coli* obtained from a commercial supplier; *see* the specification at page 46, lines 29-30), and fusion proteins were expressed and purified. The details of the purification process are provided in the specification at pages 47-48. Mice were injected with the fusion proteins obtained, as described in the specification at page 48, lines 5-14, and Applicants performed an assay, which is also described in the specification (*see* Example 2 and page 48, lines 15-26) to detect an immune

response, as evidenced by production of cytotoxic T lymphocytes (CTLs). Immunization with the fusion protein containing NP.B "results in a dramatic stimulation of specific CTL activity directed against target cells displaying the NP.B peptide" (specification at page 48, lines 2-4) and, generally, the results obtained with fusion proteins containing NP.D were similar (specification at page 48, lines 20-32).

There is no reason why one of ordinary skill in the art could not use Applicants' exemplary methods, or any others that were known in the art, to make any given fusion protein within the scope of the present claims. There is no reason why one of ordinary skill in the art could not use Applicants' exemplary methods, or any others that were known in the art, to detect an immune response in a mammal to whom a given fusion protein had been administered. These are routine methods, well within the abilities of those of ordinary skill in the art. With respect to the selection of portions of polypeptides for inclusion, guidance is provided to those of ordinary skill in the art through Applicants' specification and is otherwise publicly available. For example, Applicants selected known CTL epitope-containing portions of the influenza antigen NP and any other known epitopes (of NP or another influenza antigen) could be selected for fusion to the stress protein Applicants used or to another. As the Examiner knows, the test for undue experimentation is not merely quantitative. A considerable amount of experimentation is permissible if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. MPEP at 2164.06 citing *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489 (CCPA 1976)).

This factor -- the quantity of experimentation necessary -- consumes the majority of the Office action. The Examiner states:

> [t]here are an enormous number of polynucleotides, vectors, and host cells to be experimentally tested in order to make a useful polypeptide of a fusion protein comprising one of 7 influenza proteins (or portions thereof) in fusion with unnamed stress proteins (or portions thereof) [*sic.*] (Office action at page 3).

Regarding polynucleotides, the Examiner reviews the degenerate nature of the genetic code. As is illustrated by the Examiner's remarks, this is well understood, and it has been since

Watson and Crick discovered the nature of the double helix and their contemporaries deciphered the code in the 1950s. One of ordinary skill in the art would not have to use non-naturally occurring polynucleotide sequences at all to practice the present invention and, if they chose to do so, they could certainly substitute one codon for another to produce the same amino acid residue without resort to undue experimentation.

Regarding the proteins *per se*, the Examiner states:

> [t]he specification and claims have not disclosed what portions of the parts of the fusion protein are required for antigenicity, and to test for this factor alone relegates the experimentation to undue experimentation regarding a lack of any indication of what experimental test or assay is to be performed (Office action at page 4).

Applicants respectfully disagree. As noted above, the specification sets out, and the amended claims now require, specific antigens of not only the influenza virus, but also specific stress proteins. The sequences of these components of the claimed fusion proteins were known in the art; they were (and are) readily available. Moreover, Applicants made and successfully tested two portions of an influenza NP antigen. The test, an assay for CTLs, is well described in the specification, and those of ordinary skill in the art are quite capable of using such an assay to determine whether a given fusion protein induces an immune response.

With respect to the host cell (which is not claimed, but may be used to produce a fusion protein within the scope of the present claims), the Examiner states, "it is well known that a myriad of thousands of cell types are known to Biotechnology" (Office action at page 5). After acknowledging that "some of these known cell types are more commonly utilized" than others (Office action at page 5), the Examiner moves to a discussion of U.S. Patent No. 5,082,767, entitled "Codon Pair Utilization" (herein, "Hatfield"). This transition is not understood, as Hatfield's teaching, which concerns determining native codon pairing preferences, methods for altering a gene of a first organism for expression in a second, and similar methods, is completely independent of host cell type. Hatfield expressly states that "the present invention is not directed to or dependent on any particular expression system or technique" (Hatfield at column 11, lines 55-58). While the Examiner notes "that the instant disclosure lacks any codon pair

frequency analysis description for even a single host cell type" (Office action at page 5), this has little if any bearing on enablement. There is no reason to believe one of ordinary skill in the art would require such a teaching to practice the invention now claimed (the sufficiency of the disclosure was established above), nor is there any evidence that Hatfield's teaching is generally required in the context of fusion proteins. The U.S. Patent and Trademark Office's website currently includes at least 1,936 patents that include the term "fusion protein" in the claims. Nowhere (in no searchable field) do *any* of these patents include the term "codon pair utilization" or "codon pair" or "codon utilization" or "5,082,767" (Hatfield's patent number).

In anticipation of the present reply, the Examiner states, "Applicant may argue that inoperative subject matter is permitted in a claim" (Office action at page 6). To the contrary, claims 54 and 61 include "wherein" clauses requiring that "the fusion protein induces an immune response against the antigen in a mammal to whom the fusion protein is administered". Thus, inoperative subject matter (*i.e.*, fusion proteins that do not induce an immune response in a mammal) is not within the scope of the present claims. One of ordinary skill in the art may have to test a given fusion protein for operability, but that, for the reasons given above, does not constitute undue experimentation.

To reach a conclusion regarding enablement, the factors set out in the Examiner's action and discussed here are balanced against one another. That balance, in the present case, weighs in favor of a finding of enablement. Even if the quantity of experimentation were high, a considerable amount of experimentation is permissible if it is merely routine. Making fusion proteins is unquestionably routine, and any fusion made can be readily tested in the assay provided in the specification. The nature of the invention is quite straightforward. Applicants have invented a fusion protein that includes one of each of the two components specified, by name (*e.g.*, nucleoprotein and an Hsp100-200), in their claims. Although molecular biology techniques may be required to produce these fusion proteins, the techniques are surely among the most frequently practiced, best understood, and reliable. Nothing on the record, including Hatfield, establishes that one of ordinary skill in the art would be forced to resort to undue experimentation to make and use the fusion proteins now claimed. The state of the art is high, as

is the level of skill of those within the practice. Applicants' specification discloses more than sufficient information, including working examples demonstrating success with two fusion proteins within the scope of the claims. There is no reason to expect that others could not do the same with the same or different fusion proteins.

Finally, the analysis require reasonabless and the outcome should be consistent with articulated public policies. In *In re Forman, supra*, the court stated:

> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art (citing *Ansul Co. v. Uniroyal, Inc.*)

In *In re Goffe*, 542 F.2d 564, 567 (CCPA 1976), the court stated:

> [T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

Applicants have invented much more than the fusion proteins exemplified in the specification. If their claims were limited to those, or limited in some other substantial way, others could make and use Applicants' invention with impunity. For the reasons provided, analysis of the relevant factors weighs in favor of enablement. Applicants respectfully request reconsideration and withdrawal of this ground for rejection.

Enclosed is a check for excess claim fees and a check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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